Influenza Virus Vaccine Live, Intranasal
fluMist®
2005-2006 Formula

FOR NASAL ADMINISTRATION ONLY

Rx only

DESCRIPTION

Influenza Virus Vaccine Live, Intranasal (FluMist®) is a live trivalent nasally administered vaccine intended for active immunization for the prevention of influenza.

Each 0.5 mL dose is formulated to contain $10^{6.5-7.5}$ $TCID_{50}$ (median tissue culture infectious dose) of live attenuated influenza virus reassortants of the strains recommended by the U.S. Public Health Service (USPHS) for the 2005-2006 season: A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2), and B/Jiangsu/10/2003 (B/Shanghai/361/2002-like) [1]. These strains are (a) *antigenically representative* of influenza viruses that may circulate in humans during the 2005-2006 influenza season; (b) *cold-adapted* (*ca*) (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type viruses); (c) *temperature-sensitive (ts)* (i.e., they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (d) *attenuated (att)* so as not to produce classic influenza-like illness in the ferret model of human influenza infection. The cumulative effect of the antigenic properties and the *ca*, *ts*, and *att* phenotype is that the attenuated vaccine viruses replicate in the nasopharynx to induce protective immunity.

Each of the three influenza virus strains contained in FluMist is a genetic reassortant of a Master Donor Virus (MDV) and a wild-type influenza virus. The MDVs (A/Ann Arbor/6/60 and B/Ann Arbor/1/66) were developed by serial passage at sequentially lower temperatures in specific pathogen-free (SPF) primary chick kidney cells [2]. During this process, the MDVs acquired the *ca*, *ts* and *att* phenotype and multiple mutations in the gene segments that encode viral proteins other than the surface glycoproteins. The individual contribution of the genetic sequences of the six non-glycoprotein MDV genes ("internal gene segments") to the *ca*, *ts,* and *att* phenotype is not completely understood. However, for the Type A MDV, at least five genetic loci in three different internal gene segments contribute to the *ts* and *att* phenotype. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the *ts* and *att* properties; two additional genetic loci in a third gene segment also contribute to the *att* property. No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) (see TRANSMISSION) [3, 4]. For each of the three strains in

FluMist, the six internal gene segments responsible for *ca*, *ts*, and *att* phenotypes are derived from the MDV, and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant wild-type influenza viruses that have been recommended by the USPHS for inclusion in the annual vaccine formulation. Thus, the three viruses contained in FluMist maintain the replication characteristics and phenotypic properties of the MDV and express the HA and NA of wild-type viruses that are related to strains expected to circulate during the 2005-2006 influenza season.

Viral harvests used in the production of FluMist are produced by inoculating each of the three reassortant viruses into specific pathogen-free (SPF) eggs that are incubated to allow for vaccine virus replication. The allantoic fluid of these eggs is harvested, clarified by centrifugation, and stabilized with buffer containing sucrose, potassium phosphate, and monosodium glutamate (0.47 mg/dose). Each lot of viral harvest is tested for *ca*, *ts*, and *att* and is also tested extensively by *in vitro* and *in vivo* methods to detect adventitious agents. Viral harvests from the three strains (H1N1, H3N2, and B) are subsequently blended and diluted as required to desired potency with allantoic fluid derived from uninfected SPF eggs and/or diluted stabilizing buffer (same composition as above) to produce trivalent bulk vaccine. The bulk vaccine is then filled directly into individual sprayers for nasal administration. These sprayers are labeled and stored at ≤ -15°C.

Gentamicin sulfate is added early in the manufacturing process during preparation of reassortant viruses at a calculated concentration of approximately 1 µg/mL. Later steps of the manufacturing process do not use gentamicin, resulting in a diluted residual concentration in the final product of <0.015 µg/mL (limit of detection of the assay). FluMist does not contain any preservatives.

Each pre-filled FluMist sprayer contains a single 0.5 mL dose. The tip attached to the sprayer is equipped with a one-way valve that produces a fine mist that is primarily deposited in the nose and nasopharynx. When thawed for administration, FluMist is a colorless to pale yellow liquid and is clear to slightly cloudy (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Influenza is a highly infectious respiratory viral infection that causes recurrent winter epidemics of acute disease in persons of all ages. Highest rates of illness are generally reported among 5-14 year-olds [5, 6]. Influenza-associated deaths have been reported in previously healthy children and young adults. Among healthy individuals 15-44 years of age, the average rate of excess hospitalizations attributable to influenza is 23-25 per 100,000 per year [7], with an annual influenza-associated mortality rate of 0.2-1.5 per 100,000 person-years [8].

Types A and B influenza viruses are the principal causes of influenza in humans. Type A influenza viruses are divided into subtypes on the basis of the two surface antigens,

hemagglutinin (HA) and neuraminidase (NA), while influenza virus B is classified as a single subtype. Continuous mutation of the influenza virus genome leads to an accumulation of genetic and accompanying antigenic changes that result in the evolution of viruses into recognizable antigenic lineages or strains within a subtype. Protective immune responses following natural infection result in population-based immunity to circulating strains. However, this immune barrier eventually results in the emergence of strains that have undergone antigenic change, or "drift." Because these "drifted" strains can escape immunity to HA and NA antigens of previously circulating strains, vaccines may require annual updating to match the contemporary strains.

Vaccination is the principal means of prevention of influenza and influenza-associated complications [1].

Mechanism of Action

Immune mechanisms conferring protection against influenza following receipt of FluMist vaccine are not fully understood. Likewise, naturally acquired immunity to wild-type influenza has not been completely elucidated. Serum antibodies, mucosal antibodies and influenza-specific T cells may play a role in prevention and recovery from infection [9, 10]. Vaccination with FluMist has been demonstrated to induce influenza strain-specific serum antibodies [11, 12].

Clinical Studies

FluMist was administered to 20,228 subjects in clinical studies. The population evaluated included 10,297 healthy children 5-17 years of age (14,058 doses of FluMist received) and 3297 healthy adults 18-49 years of age (3335 doses of FluMist received) who received at least one dose of vaccine. Second and third annual doses have been given to 1766 and 128 children 5-17 years of age, respectively. In randomized, placebo-controlled trials, 4719 healthy children 5-17 years of age and 2864 healthy adults 18-49 years of age received FluMist.

The efficacy of FluMist against culture-confirmed influenza disease for Types A/H3N2 and B was assessed in a field trial in children. The effectiveness of FluMist against Types A/H3N2 and B, defined as a reduction in influenza-like illness and illness-associated health care utilization, was assessed in a field trial in adults. Type A/H1N1 did not circulate during either trial, and no field efficacy data against this strain are available.

Pediatric Study

The Pediatric Efficacy Study was a multi-center, randomized, double-blind, placebo-controlled trial performed in healthy U.S. children to evaluate the efficacy of FluMist against culture-confirmed influenza over two successive seasons [13, 14]. The primary endpoint for the first year of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza in healthy children who received two doses of vaccine. During the first year of

the study a subset of 312 children 60-71 months of age were randomized 2:1 (vaccine:placebo). All children with culture-confirmed influenza experienced respiratory symptoms (cough, runny nose, or sore throat) and most experienced fever (68%), health care provider visits (68%), and missed school days (74%).

As shown in Table 1, when compared with placebo recipients, FluMist recipients 60-71 months of age who received two doses of vaccine (n=238) experienced a significant reduction in the incidence of culture-confirmed influenza (efficacy 87.4%, 95% CI: 59.4, 97.9). In the 60-71 month old age group, children who received one dose of FluMist when compared to one dose of placebo experienced a significant reduction in the incidence of culture-confirmed influenza (0 of 54 FluMist recipients vs 3 of 20 placebo recipients; efficacy 100%, 95% CI: 47.0, 100).

Approximately 85% of the participants in the first year returned for the second year of the Pediatric Efficacy Study, including a subset of 544 children 60-84 months of age [15]. During the second year of the trial, the H3N2 strain included in the vaccine was A/Wuhan/359/95, which was antigenically distinct from the A/Sydney/05/97 H3N2 strain that was the primary circulating strain. Type A/Wuhan/359/95 (H3N2) also circulated as did Type B strains. Children remained in the same treatment group as in year one and received a single dose of FluMist or placebo. The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza after a single annual revaccination dose of FluMist.

In the subset of 544 children 60-84 months of age, illness associated with culture-confirmed illness in the second year was similar in scope and severity to that in the first year. The overall efficacy of FluMist against culture-confirmed wild-type influenza, regardless of antigenic match, was 86.9% (95% CI: 70.8, 94.1).

Table 1
Efficacy of FluMist Against Culture-Confirmed Influenza in Children ≥ 60 Months of Age

Endpoint	Cases		Efficacy (%)	(95% CI)
	FluMist	Placebo		
	N=163	**N= 75**		
Year One (60 – 71 mo of age)	**n (%)**	**n (%)**		
Culture-confirmed influenza[a]	3 (1.8)	11 (14.7)	**87.4**	(59.4, 97.9)*
	N=375	**N=169**		
Year Two (60 – 84 mo of age)	**n (%)**	**n (%)**		
Culture-confirmed influenza[a,b]	7 (1.9)	24 (14.2)	**86.9**	(70.8, 94.1)*

* Denotes statistically significant, p-value ≤0.05.

a Overall efficacy against Type A (H3N2) and Type B wild-type viruses. Field efficacy against wild Type A (H1N1) viruses could not be determined because those strains did not circulate during the study period.

b Includes illness caused by A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.

Studies in Adults

The Adult Effectiveness Study was a multi-center, randomized, double-blind, placebo-controlled trial in which healthy adults were enrolled, including 3920 adults 18-49 years of age (2150 women and 1770 men). Participants were randomized 2:1, vaccine:placebo. The trial was designed to evaluate the effectiveness of FluMist in the reduction of influenza-like illness during the peak influenza outbreak period at each site, based on community surveillance [16]. Cultures for influenza virus were not obtained from subjects in the trial, so that the efficacy against culture-confirmed influenza was not assessed. The A/Wuhan/359/95 (H3N2) strain, which was contained in FluMist, was antigenically distinct from the predominant circulating strain of influenza virus during the trial period, A/Sydney/05/97 (H3N2). Type A/Wuhan (H3N2) and Type B strains also circulated in the U.S. during the study period. The primary endpoint of the trial was the reduction in the proportion of participants with one or more episodes of any febrile illness (AFI). Two other, more specific febrile influenza-like illness definitions were also prospectively assessed: severe febrile illness (SFI), and febrile upper respiratory illness (FURI). Adults were characterized as having AFI if they had symptoms for at least two consecutive days with fever on at least one day and if they had two or more symptoms (fever, chills, headache, runny nose, sore throat, cough, muscle aches, tiredness/weakness) on at least one day. SFI was defined as having at least three consecutive days of symptoms, at least one day of fever, and two or more symptoms on at least three days. FURI was defined as at least two consecutive days of upper respiratory infection (URI) symptoms (runny nose, sore throat, or cough), fever on at least one day, and at least two URI symptoms on at least one day. Adults meeting the three illness definitions often had associated health care provider visits (25-31%), used antibiotics (28-32%), and missed at least one day of work (51-58%).

During the seven-week site-specific outbreak period, in the subset of subjects age 18-49 years, FluMist recipients did not experience a significant reduction in AFI; significant reductions were observed for SFI and FURI (Table 2). An additional measure of the severity of disease was illness-associated days of health care provider visits; FluMist recipients experienced significant reductions in days of health care provider visits associated with SFI (17.8%, 95% CI: 2.0, 31.0), and FURI (36.9%, 95% CI: 24.4, 47.3) when compared to placebo recipients. However, no significant reduction in days of health care provider visits associated with AFI was observed among FluMist recipients when compared to placebo recipients.

Table 2
Effectiveness of FluMist in Adults 18–49 Years of Age
During the 7-week Site-Specific Outbreak Period

Endpoint	FluMist N=2411[a] n (%)	Placebo N=1226[a] n (%)	Percent Reduction	(95% CI)
Participants with one or more events of:[b]				
Any febrile illness	331 (13.73)	189 (15.42)	**10.9**	(-5.1, 24.4)
Severe febrile illness	250 (10.37)	158 (12.89)	**19.5**	(3.0, 33.2)*
Febrile upper respiratory illness	213 (8.83)	142 (11.58)	**23.7**	(6.7, 37.5)*

* Denotes p-value ≤0.05.

Note: The proportion of participants with any febrile illness (AFI) was the primary study endpoint; effectiveness was not demonstrated for this endpoint (p-value >0.05).

[a] Number of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively).

[b] The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.

Challenge Study

The ability of FluMist to protect adults from influenza illness after challenge with wild-type influenza was assessed in a multi-center, randomized, double-blind, placebo-controlled trial in healthy adults 18-41 years of age who were serosusceptible to at least one strain included in the vaccine [12]. Adults were randomized to receive FluMist (n=29) or placebo (n=31). Each subject was challenged intranasally with only a single strain of wild-type virus (Type A/H3N2, Type A/H1N1 or Type B) to which he/she was serosusceptible, and the results were pooled for all three strains combined within each treatment group. Laboratory-documented influenza illness due to all three strains combined was reduced compared to placebo by 85% (95% CI: 28, 100) in FluMist recipients.

Study in Adults with Human Immunodeficiency Virus (HIV) Infection

Safety and shedding of vaccine virus following FluMist administration were evaluated in HIV-infected (N=57) and HIV-negative (N=54) adults 18-58 years of age in a randomized, double-blind, placebo controlled trial [17]. HIV-infected participants had CD4 counts ≥200 cells/mm^3 [median = 604 cells/mm^3 for FluMist (N=28) and 508 cells/mm^3 for placebo (N=26)] and were asymptomatic or mildly symptomatic (CDC Class A1-2). Reactogenicity events were monitored for 10 days post-vaccination. Nasal swabs for viral culture were obtained on three occasions (Days 3-5, 7-10 and 28-35). Runny nose/nasal congestion was observed more frequently in FluMist recipients in both the HIV-infected (FluMist = 61% vs. placebo = 31%) and HIV-negative (FluMist = 78% vs. placebo = 44%) groups (unadjusted $p < 0.05$). No serious adverse events were reported during the one-month follow-up period. Meaningful comparisons of other adverse events were limited by the small sample size. Vaccine strain virus was detected in 1 of 28 HIV-infected (Type B on Day 5, subsequent cultures negative) and none of the HIV-negative FluMist recipients. No adverse effects on HIV viral load or CD4 counts were identified following FluMist. The efficacy/effectiveness of FluMist in preventing influenza illness in HIV-infected individuals has not been evaluated.

Transmission

FluMist contains live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients. The relationship of viral replication in a vaccine recipient and transmission of vaccine viruses to other individuals has not been established.

A prospective, randomized, double-blind, placebo-controlled trial in a daycare setting in children less than three years of age was performed with the primary objective of assessing the probability that vaccine viruses will be transmitted from a vaccinated individual to a non-vaccinated individual [18]. Children enrolled in the study attended daycare at least three days per week for four hours per day, and were in a playroom with at least four children, at least one of whom was vaccinated with FluMist. A total of 197 children 8-36 months of age were randomized to receive one dose of FluMist (n=98) or placebo (n=99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens obtained from each subject approximately three times per week. Wild-type A (H3N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Type A (H1N1) and Type B strains did not.

At least one vaccine strain was isolated from 80% of FluMist recipients. Viruses were recovered from specimens obtained over a range of 1-21 days (mean duration of 7.6 days ± 3.4 days). The cold-adapted (*ca)* and temperature-sensitive (*ts)* phenotypes were preserved in all recovered

viruses tested (n=135 tested of 250 strains isolated at the local laboratory). Ten influenza isolates were cultured from a total of seven placebo subjects. One placebo subject became infected with a Type B virus confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. Of the 11 nasal swabs obtained from the subject on Days 0-21, vaccine virus was cultured only from the Day 15 specimen. This Type B isolate retained the *ca*, *ts*, and *att* phenotypes of the vaccine strain, and had the same genetic sequence when compared to a Type B virus cultured from a vaccine recipient within the same playgroup. This placebo recipient experienced cough, coryza, and irritability similar to the symptoms observed among some FluMist vaccinees in the trial. No viruses were cultured from any of the other placebo recipients in this playgroup. Nine isolates identified as Type A were cultured from six placebo subjects; two of these subjects had two cultures that grew Type A strains (four isolates) confirmed as wild-type A/Panama (H3N2). Type A isolates that could not be further characterized were cultured from the four remaining placebo subjects; because the isolates could not be further characterized, the possibility that they were vaccine strains could not be excluded.

Assuming that a single transmission event occurred (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a single FluMist vaccinee in this daycare setting was 0.58% (95% CI: 0, 1.7) based on the Reed Frost model [19]. With documented transmission of one Type B in one placebo subject and possible transmission of Type A viruses in four placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6), using the Reed Frost model.

The duration of FluMist vaccine virus replication and the potential for transmission of vaccine viruses by recipients 5-49 years of age have not been established.

INDICATIONS AND USAGE

FOR NASAL ADMINISTRATION ONLY

FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age.

FluMist is not indicated for immunization of individuals less than 5 years of age, or 50 years of age and older, or for therapy of influenza, nor will it protect against infections and illness caused by infectious agents other than influenza A or B viruses.

CONTRAINDICATIONS

Under no circumstances should FluMist® be administered parenterally.

Individuals with a history of hypersensitivity, especially anaphylactic reactions, to any component of FluMist, including eggs or egg products, should not receive FluMist (see DESCRIPTION).

FluMist is contraindicated in children and adolescents (5-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye syndrome with aspirin and wild-type influenza infection.

FluMist should not be administered to individuals who have a history of Guillain-Barré syndrome.

As with other live virus vaccines, FluMist should not be administered to individuals with known or suspected immune deficiency diseases such as combined immunodeficiency, agammaglobulinemia, and thymic abnormalities and conditions such as human immunodeficiency virus infection, malignancy, leukemia, or lymphoma. FluMist is also contraindicated in patients who may be immunosuppressed or have altered or compromised immune status as a consequence of treatment with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies.

WARNINGS

The safety of FluMist in individuals with asthma or reactive airways disease has not been established. In a large safety study in children 1-17 years of age, children <5 years of age who received FluMist were found to have an increased rate of medically attended events, coded as asthma/reactive airway disease within 42 days of vaccination when compared to placebo recipients (see ADVERSE REACTIONS). FluMist should not be administered to individuals with a history of asthma or reactive airways disease.

The safety of FluMist in individuals with underlying medical conditions that may predispose them to severe disease following wild-type influenza infection has not been established. FluMist is not indicated for these individuals. High-risk individuals include, but are not limited to, adults and children with chronic disorders of the cardiovascular and pulmonary systems, including asthma; pregnant women; adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes), renal dysfunction, or hemoglobinopathies; and adults and children with congenital or acquired immunosuppression caused by underlying disease or immunosuppressive therapy (see CONTRAINDICATIONS). Intramuscularly administered inactivated influenza vaccines are available to immunize high-risk individuals [1].

As with any vaccine, FluMist may not protect 100% of individuals receiving the vaccine.

PRECAUTIONS

General

CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR THE SAFE AND EFFECTIVE USE OF THIS PRODUCT.

Prior to administration of FluMist, individuals or their parent/guardian should be asked about their current health status and their personal medical history, including immune status, to determine the existence of any contraindications to immunization with FluMist (see CONTRAINDICATIONS and WARNINGS). FluMist recipients should avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. The safety of FluMist has been studied in 57 asymptomatic or mildly symptomatic adults with HIV infection (see CLINICAL STUDIES).

EPINEPHRINE INJECTION (1:1000) OR COMPARABLE TREATMENT MUST BE READILY AVAILABLE IN THE EVENT OF AN ACUTE ANAPHYLACTIC REACTION FOLLOWING VACCINATION. The health care provider should ensure prevention of any allergic or other adverse reactions by reviewing the individual's history for possible sensitivity to influenza vaccine components, including eggs and egg products.

Administration of FluMist should be postponed until after the acute phase (at least 72 hours) of febrile and/or respiratory illnesses.

Information for Vaccine Recipients or Parents/Guardians

Vaccine recipients or their parents/guardians should be informed by the health care provider of the potential benefits and risks of FluMist, and the need for two doses for the first use of FluMist in 5-8 year olds. Due to the possible transmission of vaccine virus, vaccine recipients or their parents/guardians should be advised that vaccine recipients should avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days.

The vaccine recipient or the parent/guardian accompanying the vaccine recipient should be told to report any suspected adverse events to the physician or clinic where the vaccine was administered (see ADVERSE EVENT REPORTING).

Drug Interactions

Children or adolescents who are receiving aspirin therapy or aspirin-containing therapy should not receive FluMist (see CONTRAINDICATIONS). FluMist should not be administered to persons on immunosuppressive therapy.

The concurrent use of FluMist with antiviral compounds that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for interference between such compounds and FluMist, it is advisable not to administer FluMist until 48 hours after the

cessation of antiviral therapy and that antiviral agents not be administered until two weeks after administration of FluMist unless medically indicated.

There are no data regarding co-administration of FluMist with other intranasal preparations, including steroids.

Concurrent Administration with Other Vaccines

The safety and immunogenicity of FluMist when administered concurrently with other vaccines have not been determined. Studies of FluMist in healthy individuals excluded subjects who received any live virus vaccine within one month of enrollment and any inactivated or subunit vaccine within two weeks of enrollment. Therefore, healthcare providers should consider the risks and benefits of concurrent administration of FluMist with other vaccines.

Laboratory Interactions

Data related to the length of time that FluMist can be recovered from nasal specimens of children and adults are limited. Nasopharyngeal secretions or swabs collected from vaccinees may test positive for influenza virus for up to three weeks.

Carcinogenesis, Mutagenesis, Impairment of Fertility

FluMist has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

Pregnancy (Category C)

Animal reproduction studies have not been conducted with FluMist. It is also not known whether FluMist can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Therefore, FluMist should not be administered to pregnant women.

Nursing Mothers

It is not known whether FluMist is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if FluMist is administered to nursing mothers.

Pediatric Use

The safety of FluMist in infants and children <60 months of age has not been established (see CLINICAL STUDIES, INDICATIONS AND USAGE, and ADVERSE REACTIONS).

Geriatric Use

Clinical studies with FluMist did not include sufficient numbers of adults age 65 years and older to determine if they respond differently from younger individuals. The safe use of FluMist in persons

65 years and older has not been established (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

See CLINICAL STUDIES for a description of the number of participants in clinical trials.

Serious Adverse Events

Across all clinical trials, serious adverse events (SAEs) were monitored after vaccination for 42 days in children and for 28 days in adults. SAEs occurred at a similar rate (<1%) in FluMist and placebo recipients for both healthy children and healthy adults.

Overall, across the placebo-controlled trials in adults and children, the incidence of selected adverse reactions that may be complications of wild-type influenza (such as pneumonia, bronchitis, bronchiolitis, or central nervous system events) was similar in FluMist and placebo groups.

Adverse Events in Placebo-Controlled Trials

In all placebo-controlled studies, allantoic fluid from uninfected eggs was used as the placebo. In randomized, placebo-controlled trials, 4719 healthy children 5-17 years of age and 2864 healthy adults 18-49 years of age received FluMist and 2327 healthy children and 1454 healthy adults received the placebo. In placebo-controlled clinical trials conducted in healthy populations, solicited adverse events and daily temperatures were collected on diary cards. These solicited events included runny nose/nasal congestion, sore throat, cough, irritability, headache, chills, vomiting, muscle aches, and decreased activity and a feeling of tiredness/weakness.

Solicited Adverse Events in Children

Table 3 shows an analysis of solicited events for the Pediatric Efficacy Study in the subset of healthy children 60-71 months of age. The largest absolute differences between FluMist and placebo after Dose One were observed in the incidences of headache and runny nose/nasal congestion. No differences were observed for fever (>100°F oral). Following Dose Two, the largest absolute differences between FluMist and placebo were runny nose/nasal congestion and cough. There was no significant increase in influenza-like illness (ILI) as defined by the CDC in the FluMist group compared to the placebo group. CDC has defined CDC-ILI as having fever (temperature ≥100°F oral) plus either cough or sore throat on the same day or on consecutive days.

Table 3
Summary of Solicited Events Observed within 10 Days after Each Dose for Vaccine and Placebo Recipients; Healthy Children 60–71 Months of Age

	Post-Dose One		Post-Dose Two	
	FluMist	**Placebo**	**FluMist**	**Placebo**
	214[a]	95[a]	161[a]	75[a]
Event	**%**	**%**	**%**	**%**
Any event	65.0	62.1	66.5	53.3
Cough	25.7	32.6	38.5	30.7
Runny Nose/ Nasal Congestion	48.1	44.2	46.0	32.0
Sore Throat	12.6	18.9	9.3	16.0
Irritability	17.8	15.8	9.9	9.3
Headache	17.8	11.6	6.8	16.0
Chills	6.1	5.3	2.5	4.0
Vomiting	4.7	3.2	5.6	12.0
Muscle Aches	6.1	4.2	5.0	4.0
Decreased Activity	14.0	12.6	10.6	13.3
Fever[b]				
Temp 1	10.3	9.5	4.3	4.0
Temp 2	2.3	2.1	0.6	1.3
Temp 3	0.0	0.0	0.0	0.0

Note: There were no statistically significant differences in any of these events (p-value >0.05); Fisher's Exact method.

[a] Number of evaluable subjects (those who returned diary cards) for each event.

[b] Fever
Temp 1: Oral >100°F, rectal or aural >100.6°F, or axillary >99.6°F.
Temp 2: Oral >102°F, rectal or aural >102.6°F, or axillary >101.6°F.
Temp 3: Oral >104°F, rectal or aural >104.6°F, or axillary >103.6°F.

For the cohort of 128 children who received FluMist across three consecutive years, rates of solicited adverse events were not significantly increased when compared to placebo recipients [15].

Medically Attended Events in Children and Adolescents

A large randomized, double-blind, placebo-controlled trial in healthy children 1 through 17 years of age was conducted at 31 clinics in the Northern California Kaiser-Permanente Health Maintenance Organization (HMO) to assess the rate of medically attended events (MAEs) within 42 days of vaccination. Participants were randomized 2:1 (vaccine:placebo). A total of 6657 evaluable children 5-17 years of age were enrolled, including 3244 boys and 3413 girls. Of these

6657 children, 2606 were 5-8 years of age and 4051 were 9-17 years of age. Dose Two for children less than nine years of age was to be administered 28 to 42 days after Dose One.

Data regarding MAEs were obtained from the Kaiser-Permanente computerized health care utilization databases for hospitalizations, emergency department visits and clinical visits. MAEs were analyzed individually and within four pre-specified grouped diagnoses: acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza. For these four pre-specified grouped diagnoses, no significant increase in risk for FluMist recipients was seen in the combined analyses across all utilization settings, doses, and age groups. Selected respiratory tract illnesses of special interest (pneumonia, bronchitis, bronchiolitis, and croup) were included in acute respiratory tract events and were not associated with increased risk for FluMist recipients in any protocol-specified analysis. No systemic bacterial infection occurred. In FluMist recipients, an increased risk was not observed for rare events that have been reported with naturally occurring influenza virus infection, including seizures, febrile seizures, and epilepsy. No cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or myocarditis (influenza-associated rare disorders) were reported in this study.

In this study, in individuals 5-17 years of age, four individual MAEs were significantly increased and 11 were significantly decreased. Of the four individual MAEs associated with increased risk, a biological association with FluMist is plausible for one: abdominal pain. Of the 11 individual MAEs associated with decreased risk, a biologically plausible association with FluMist exists for seven: asthma, bronchitis, conjunctivitis, cough, viral syndrome, otitis media, and wheezing/shortness of breath. However, in the same study, a statistically significant increase in asthma or reactive airways disease was observed for children 12-59 months of age following Dose One (Relative Risk 3.53, 90% CI: 1.1, 15.7). As a result of this finding, FluMist is not indicated for children <60 months of age.

Solicited Adverse Events in Adults

In the placebo-controlled Adult Effectiveness Study, the rates of solicited adverse events in the subset of healthy adults 18-49 years of age are shown in Table 4. Statistically significant differences were observed for any event, cough, runny nose, sore throat, chills, and tiredness/weakness. Fever >100°F was similar in FluMist and placebo recipients after a single dose. There was no significant increase in influenza-like illness (ILI) as defined by the CDC in the FluMist group compared to the placebo group.

Table 4
Summary of Solicited Events Observed within 7 Days after Each Dose for Vaccine and Placebo Recipients; Healthy Adults 18–49 Years of Age

	FluMist N=2548[a]	Placebo N=1290[a]
Event	**(%)**	**(%)**
Any event	71.9*	62.6
Cough	13.9*	10.8
Runny Nose	44.5*	27.1
Sore Throat	27.8*	17.1
Headache	40.4	38.4
Chills	8.6*	6.0
Muscle Aches	16.7	14.6
Tiredness/Weakness	25.7*	21.6
Fever		
Oral Temp >100°F	1.5	1.3
Oral Temp >101°F	0.5	0.7
Oral Temp >102°F	0.1	0.2
Oral Temp >103°F	0.0	0.0

* Denotes statistically significant p-value ≤0.05; no adjustments for multiple comparisons; Fisher's Exact Method.

a Number of evaluable subjects (those who returned diary cards). [97.9% of FluMist recipients and 97.9% of placebo recipients.]

Other Adverse Events in Children and Adults

In addition to the solicited events, parents of subjects in the Pediatric Efficacy Trial also reported other adverse events that occurred during the course of the trial. Among healthy children age 60-71 months, the events that occurred in at least 1% of FluMist recipients and at a higher rate compared to placebo were: abdominal pain (3.7% FluMist vs 0% placebo), otitis media (1.4% FluMist vs 0% placebo), accidental injury (2.3% FluMist vs 2.1% placebo), diarrhea (3.7% FluMist vs 1.1% placebo), following Dose One and otitis media (3.1% FluMist vs 1.3% placebo) following Dose Two. None of these differences were statistically significant.

In addition to the solicited events, adults who participated in the Adult Effectiveness Study also reported other adverse events that occurred during the course of the clinical trial. For adults 18-49 years of age in the Adult Effectiveness Study, nasal congestion (9.2% FluMist vs 2.2% placebo), rhinitis (6.3% FluMist vs 3.1% placebo), and sinusitis (4.1% FluMist vs 2.2% placebo) were reported significantly more often by FluMist recipients compared to placebo recipients.

Adverse events reported post-licensure have included nausea, rash, epistaxis, and hypersensitivity reactions (including anaphylaxis, facial edema, and urticaria). These events occurred at similar rates in FluMist versus placebo recipients in pre-licensure studies.

Annually, 20-40 cases of Guillain-Barré syndrome (GBS) that occur within 42 days of administration of inactivated influenza vaccine are reported to VAERS. Although cases of GBS with temporal association with FluMist have been very rarely reported evidence of a causal relationship to influenza vaccines, including FluMist, has not been established.

Guillain-Barré Syndrome and Influenza Vaccines

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was <10 cases/1 million persons vaccinated with the risk for influenza vaccine-associated GBS higher among persons aged >25 years than persons <25 years. Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10-20 cases/1 million adults. Thus, investigations to date indicate no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that, if influenza vaccine does pose a risk, it is probably slightly more than one additional case/1 million persons vaccinated. Cases of GBS after influenza infection have been reported, but no epidemiologic studies have documented such an association [1].

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history. Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome [1].

ADVERSE EVENT REPORTING

Reporting by vaccine recipients or the parents/guardians of vaccinees and health care providers of all adverse events occurring after vaccine administration is encouraged. The U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the FDA Web site at: http://www.vaers.org.

DOSAGE AND ADMINISTRATION

FOR NASAL USE ONLY. DO NOT ADMINISTER PARENTERALLY.

FluMist® should be administered according to the following schedule:

Age Group	Vaccination Status	Dosage Schedule
Children age 5 years through 8 years	Not previously vaccinated with FluMist	2 doses (0.5 mL each, 60 days apart ± 14 days) for initial season
Children age 5 years through 8 years	Previously vaccinated with FluMist	1 dose (0.5 mL) per season
Children and Adults age 9 through 49 years	Not applicable	1 dose (0.5 mL) per season

For healthy children age 5 years through 8 years who have not previously received FluMist vaccine, the recommended dosage schedule for nasal administration is one 0.5 mL dose followed by a second 0.5 mL dose given at least 6 weeks later. Only limited data are available on the degree of protection in children who receive one dose (see CLINICAL PHARMACOLOGY).

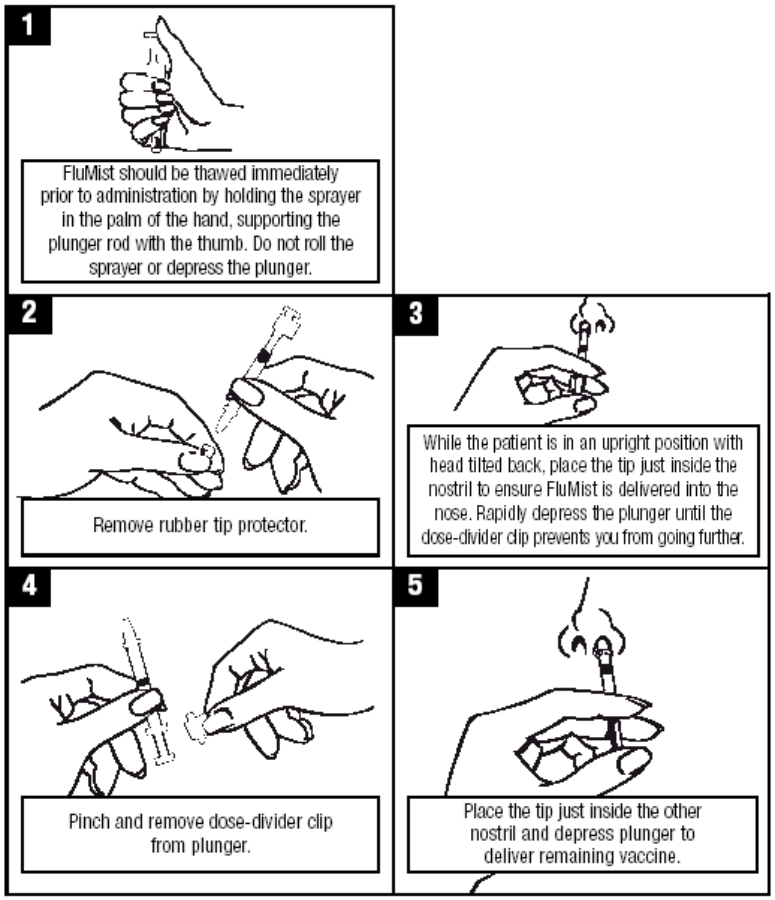
For all other healthy individuals, including children age 5-8 years who have previously received at least one dose of FluMist, the recommended schedule is one dose.

FluMist should be administered prior to exposure to influenza. The peak of influenza activity is variable from year to year, but generally occurs in the U.S. between late December and early March. Because the duration of protection induced by FluMist over multiple seasons is not known and yearly antigenic variation in the influenza strains is possible, annual revaccination may increase the likelihood of protection.

FluMist must be thawed prior to administration. FluMist may be thawed by holding the sprayer in the palm of the hand and supporting the plunger rod with the thumb (see ADMINISTRATION INSTRUCTIONS); the vaccine should be administered immediately thereafter. Alternatively, FluMist may be thawed in a refrigerator and stored at 2-8°C (36-46°F) for no more than 60 hours prior to use. When thawed for administration, FluMist is a colorless to pale yellow liquid and is clear to slightly cloudy; some proteinaceous particulates may be present but do not affect the use of the product.

Approximately 0.25 mL (i.e., half of the dose from a single FluMist sprayer) is administered into each nostril while the recipient is in an upright position. Insert the tip of the sprayer just inside the nose and depress the plunger to spray. The dose-divider clip is removed from the sprayer to administer the second half of the dose (approximately 0.25 mL) into the other nostril. Once FluMist has been administered, the sprayer should be disposed of according to the standard procedures for medical waste.

ADMINISTRATION INSTRUCTIONS



HOW SUPPLIED

FluMist is supplied for intranasal delivery in a package of 10 pre-filled, single-use sprayers NDC 66019-102-01

NDC 66019-103-01 – For Sample use only

STORAGE

STORE AT OR BELOW -15°C (5°F).

DO NOT REFREEZE AFTER THAWING.

UPON RECEIPT, FluMist SHOULD BE IMMEDIATELY STORED FROZEN AT -15°C (5°F) OR BELOW.

FluMist **SHOULD BE STORED FROZEN** at an average temperature of -15°C (+5°F) or colder. Any freezer (e.g., chest, frost-free) that reliably maintains an average temperature of -15°C and has a separate sealed freezer door is acceptable for storing FluMist.

FluMist may be thawed in a refrigerator and stored at 2-8°C (36-46°F) for no more than 60 hours prior to use.

The cold chain must be maintained when transporting FluMist prior to use.

For information regarding product storage and stability under conditions other than those recommended, call 1-877-FLUMIST.

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